3.23 Perspectives on Auditory Neuropathy: Disorders of Inner Hair Cell, Auditory Nerve, and Their Synapse

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3.23.1 Introduction

The term auditory neuropathy (Starr, A. *et al.*, 1996) was first used to describe a hearing disorder due to altered function of the auditory nerve in the presence of preserved functions of cochlear outer hair cells (OHCs; Starr, A. *et al.*, 1991). The hearing loss has specific features reflecting impairment of auditory temporal processes that are typically unaffected with sensory outer hair disturbances (Zeng, F. G. *et al.*, 1999). The disorder has also been referred to as type I afferent neuron dysfunction (Berlin, C. I. *et al.*, 1993), auditory neuropathy/auditory dys-synchrony (Berlin, C. I. *et al.*, 2003), and neural hearing loss (Rapin, I. and Gravel, J., 2003). We now know that dysfunction of the auditory nerve, having quite similar clinical features, accompanies a variety of disorders acting on the nerve, the inner hair cell, and/or their synapse. We will refer to the disorder as auditory neuropathy and emphasize whenever possible the site(s) of involvement in the auditory periphery. We will review how the varieties of auditory neuropathy are identified, the special psychoacoustic features of the hearing loss, candidate pathophysiological mechanisms, and cochlear and auditory nerve pathologies. We will introduce recent advances in knowledge of molecular organization of cochlear inner hair cell synapses and auditory nerve that suggest some mechanisms likely to be involved in auditory nerve dysfunction.

3.23.2 Testing for Auditory Neuropathy

Auditory brainstem responses (ABRs) are the far-field reflection of potentials arising in the cochlea, auditory nerve, and auditory brainstem pathways during the first 10–15 ms after a transient acoustic signal. These potentials are of small amplitude in humans (<0.5 μV) and their resolution requires averaging brain activity to several thousand acoustic stimuli. Those potentials that are time-locked to the stimuli appear in the averaged ABR whereas potentials that are not sufficiently time-locked to the acoustic signals are attenuated. The averaged ABR is therefore especially sensitive to the temporal pattern of neural discharge in auditory nerve and brainstem auditory pathways.

The ABR has five major components, labeled in sequence by Roman numerals I through V, which are generated by distinct regions of the auditory pathway. The absolute latencies of the components change with signal intensity but the time difference between each of the components remains relatively

constant independent of stimulus intensity (Starr, A. and Achor, J., 1975). Wave I is generated in the distal portions of auditory nerve in the region of the ganglion cells; wave II is generated in the proximal portions of the auditory nerve in the region of its entry into the brainstem; wave III is generated in the region of the ipsilateral cochlear nucleus; waves IV and V are generated bilaterally in the region of the midbrain tegmentum (Starr, A. and Achor, J., 1975; Starr, A. and Hamilton, A. E., 1976; Martin, W. H. *et al.*, 1995; Melcher, J. R. *et al.*, 1996). Thus the ABR components provide a longitudinal view of sequential activities arising from both the auditory nerve and brainstem portions of the auditory pathway.

Cochlear microphonics (CMs) are receptor potentials generated by both inner and OHCs. Since the dominant type of hair cell is outer, one would expect that the amplitude of cochlear microphonics derives predominantly from outer rather than inner hair cells. that can also be identified in the ABR by separately averaging potentials to condensation and rarefaction stimuli to define phase reversed components in the two averages (Starr, A. *et al.*, 1991; Berlin, C. I. *et al.*, 1998). If the condensation and rarefaction stimuli are presented in an alternating fashion, the CMs to each polarity stimulus cancel and do not appear in the ABR average.

Otoacoustic emissions (OAEs) are faint sounds produced by OHCs (Kemp, D. T., 1978; Brownell, W. E., 1984) that can be recorded by a small microphone in the ear canal and provide a measure of mechanical activity (electromotility) of cochlear OHCs.

By combining measures of ABRs, CMs, and OAEs, the site(s) of altered functions can be identified as affecting one or several of the components comprising the auditory periphery including OHCs, auditory nerve, and auditory brainstem structures. At present, there are no physiological measures available for clinical applications that are specific for identifying disorders of inner hair cells (IHCs) or their pre- and postsynaptic functions with auditory nerve.

3.23.3 Clinical Features of Auditory Neuropathy

The ABR was introduced in the 1970s as a screening method to identify auditory impairments in neonates and children (Hecox, K. and Galambos, R., 1974). There were occasional observations that ABRs could be absent even though the subject was subsequently shown to have preserved hearing by behavioral measures (Davis, H. and Hirsh, S. K., 1979; Kaga, K. *et al.*, 1979; Worthington, D. W. and Peters, J. F., 1980; Lenhardt, M. L., 1981). These authors recognized the paradox these findings posed and suggested explanations ranging from technical limitations of the ABR as a test of hearing to the possibility that the abnormal ABRs might reflect a particular kind of peripheral auditory disorder (Kraus, N. *et al.*, 1984).

Special patients can occasionally provide a solution to clinical paradoxes. We examined such a subject (Starr, A. *et al.*, 1991) identified by her teachers as possibly having a hearing problem. Audiological measures showed absent ABRs inconsistent with the mild low-frequency threshold loss. Speech comprehension was impaired and acoustic middle ear muscle reflexes were absent. When ABRs were tested separately to condensation or rarefaction clicks, short latency components appeared that were phased reversed when the two averages were superimposed consistent with their being CMs rather than neural components. OAEs were also present. Figure 1 contains the test results (audiograms, ABRs, CMs, OAEs, and cortical-evoked potentials) for another patient with the same disorder showing a mild threshold elevation (in this example affecting high frequencies), impaired speech comprehension out-of-proportion to the pure tone threshold elevation, a low amplitude and delayed wave V, and preserved hair cell measures of both CMs and OAEs. The test results for a subject with normal hearing are shown for comparison in Figure 1. The results obtained from the patient were consistent with preserved functions of cochlear OHC functions (normal CMs and OAEs) but impaired function of auditory nerve and brainstem. The failure to obtain an averaged ABR was attributed to altered synchrony of neural activity of auditory nerve rather than to a loss of auditory nerve activity because hearing thresholds were only modestly impaired. Auditory cortical-evoked potentials were present suggesting that neural synchrony was still sufficiently preserved to allow an averaged cortical response to be detected. Finally, psychoacoustic studies in this patient (Starr, A. *et al.*, 1991) and subsequently in others (Zeng, F. G. *et al.*, 1999; 2005) summarized below in this chapter revealed that the hearing disorder is indeed relatively specific for auditory percepts dependent on temporal cues (e.g., speech comprehension, gap detection, masking level differences, and low-frequency difference limens) whereas percepts dependent on intensity cues were normal. The disorder appeared

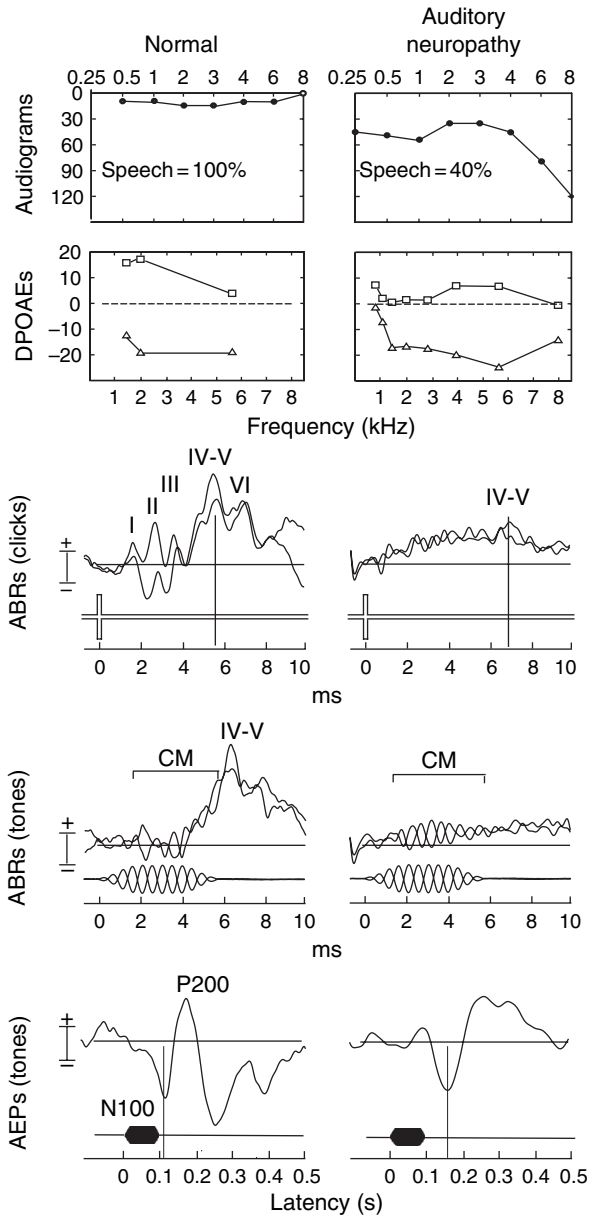

Figure 1 The audiogram (with speech comprehension), distortion product otoacoustic emissions (DPOAEs), auditory brainstem responses (ABRs) to clicks of opposite polarity, ABRs to brief tones (1 kHz) of opposite polarity and auditory cortical-evoked potentials (AEPs) to a 100 ms 1 kHz tone burst are shown for a normal-hearing and auditory neuropathy subjects. The analog stimuli used for the electrophysiological procedures are depicted below the averaged responses. The patient displays a moderate low-frequency threshold elevation that becomes less affected in mid-frequencies, and severe at high frequency (8 kHz). DPOAEs and cochlear microphonics (CMs) are present whereas only a low amplitude delayed wave V can be seen in the click-evoked ABR. The auditory cortical N100 component is present in the patient of delayed latency (160 ms) compared to the N100 in normal hearing subject (N100). Amplitude calibration is 0.25 μV for ABRs and 5 μV for AEPs.

to involve the auditory nerve and/or its synapses with inner hair cells while sparing cochlear OHCs.

Soon, additional subjects with absent ABRs and preserved OAEs and/or CMs were identified. Neurological studies of 11 adolescent and adult subjects with absent ABRs and preserved OHC activity revealed the presence of a peripheral neuropathy in eight, consistent with the presence of a concomitant neuropathy of the auditory nerve (Starr, A. *et al.*, 1996). Subsequently, the temporal bone of a subject with

neural hearing loss and peripheral neuropathy due to a mutation of the *MPZ* gene was examined and revealed marked depletion of auditory neurons with preservation of both inner and OHCs (Starr, A. *et al.*, 2003). The pathological changes in the peripheral sensory nerves and the auditory nerve were similar and consisted of nerve fiber loss (deafferentation) as well as demyelination and incomplete remyelination of the remaining fibers. These results indicate that a hearing loss characterized by a temporal processing disorder, absent ABRs, preserved OAEs and CMs can be a consequence of a neuropathy of the auditory nerve. Both Hallpike C. S. *et al.* (1980) and Spoendlin H. (1974) reported similar temporal bone findings 30 years earlier, in individuals with deafness and hereditary peripheral neuropathies. Satya-Murti S. *et al.* (1980) showed ABRs were absent or severely abnormal in subjects with hereditary neuropathy due to Fredreichs' ataxia and interpreted their findings as reflecting a disorder of the VIII nerve. Thus both a loss of fibers (deafferentation) and/or altered synchrony of nerve impulses in the remaining fibers due to demyelination and incomplete remyelination are likely factors contributing to the temporal processing defects in auditory neuropathy.

Disorders of inner hair cells and their synapses with auditory nerve fibers can also lead to a hearing disorder that is essentially indistinguishable clinically from that accompanying a neuropathy of the auditory nerve. An example of such an inner hair cell disorder occurs with mutations of genes encoding otoferlin (*OTOF*), a putative synaptic protein identified in inner hair cells (Yasunaga, S. *et al.*, 1999; Rodriguez-Ballesteros, M. *et al.*, 2003; Varga, R. *et al.*, 2003). These patients have absent ABRs and in some, preserved OAEs. The hearing loss is severe-to-profound and speech comprehension is a major impairment. Otoferlin belongs to the family of the FER-1 like proteins which are involved in membrane trafficking. Thus the some clinical findings are present with disorders of the nerve and in Otoferlin disorder of inner hair cells. It is likely that a synaptic disorder underlies the hearing loss in these patients, who do not have any evidence of peripheral or other cranial neuropathies.

The findings of auditory neuropathy and Otoferlin inner hair cell disorder (absence of ABRs with preserved OHC functions) are also recognized at high incidence in newborns tested as part of universal infant hearing screening evaluation (Kraus, N. *et al.*, 1984; Doyle, K. J. *et al.*, 1998). It is likely that many of these infants have disorders of both inner hair cells affecting synaptic function and auditory nerves due to metabolic disorders such as hypoxia, hyperbilirubinemia, infections, and prematurity. The infants are typically without clinical evidence of a peripheral neuropathy. In a study of temporal bones of premature infants dying with abnormal ABRs (OAEs were not tested) there were several who showed isolated loss of inner hair cells with preservation of both auditory ganglion cells and OHCs (Amatuzzi, M. G. *et al.*, 2001).

Thus, auditory neuropathy with quite similar physiological and audiological findings can occur as a consequence of pathology of inner hair cell, their synapses, and/or the auditory nerve due to a host of etiologies (Starr, A. *et al.*, 2001a). The common denominators are absence or profound abnormalities of ABRs, absence or profound abnormalities of acoustic reflexes of middle ear muscles and olivocochlear bundle (OCB; Berlin, C. I. *et al.*, 1993), and impaired perceptions dependent on temporal cues. Both the physiological expressions and the types of hearing impairment are remarkably similar whether the disorder is at the inner hair cell, its synapses, or the auditory nerve.

3.23.4 Exceptions to the Criteria for Defining Auditory Neuropathy

The criteria for defining auditory neuropathy have exceptions. First, ABRs are not always absent and a delayed wave V can be defined in approximately 40% of subjects. However, the changes of wave V are beyond those expected for the degree of hearing loss. Second, while it is typical to find absent acoustic middle ear muscle and efferent OCB reflexes, there are some subjects who show the reflexes to be present at elevated thresholds. Third, the impairment of speech comprehension may only be manifest in the presence of noise. Fourth, while OAEs and/or CMs are typically preserved, almost one-third of subjects show OAEs to be absent on retesting. And fifth, while hearing aid amplification is typically without benefit for understanding speech in most subjects, occasionally there are exceptions that do benefit.

The disorder can occur across the age spectrum (Hood, L. J. and Berlin, C. I., 2001; Sininger, Y. and Oba, S., 2001) reflecting a host of etiologies (e.g., hereditary, infectious, and metabolic) and risk factors (hypoxia and hyperbilirubinemia). Almost half of patients cannot be assigned an etiology. The high incidence in neonates and in children at entry to school likely reflects the use of universal auditory screening in neonates (OAEs and/or ABRs) and universal behavioral auditory testing (audiograms) in schools.

The clinical and physiological findings originally used for identifying auditory neuropathy can change over time. Audiograms and speech comprehension decline or remain stationary (Sininger, Y. and Oba, S., 2001). There are documented instances of improvement of ABRs in newborn infants after discharge from the neonatal intensive care unit and even recovery in adults affected with immune disorders acting on nerve fiber (e.g., Guillain-Barré syndrome; Ropper, A. H. and Chiappa, K. H., 1986). OAEs that are present initially may not be obtainable in approximately 30% of subjects (Starr, A. *et al.*, 2001b). CMs appear to persist longer but they too can become attenuated and difficult to detect when patients are over the age of 50 years (Starr, A., *et al.*, 2001b). These findings are consistent with the idea that some forms of auditory neuropathy may be progressive and in others also involve OHC functions.

3.23.5 Pathophysiology of Auditory Neuropathy

The remarkable similarity of electrophysiological findings in subjects with different forms of auditory neuropathy suggests a common pathophysiology independent of site of affliction. Each IHC forms separate synaptic contacts with several afferent fibers. Each of these synapses consists of the presynaptic ribbon-containing active zone and a small (~1 μm) dendritic swelling. Each active zone contains up to 80 $Ca_V1.3$ Ca^{2+} channels and approximately 60 readily releasable glutamate-containing synaptic vesicles, several of which can be released in parallel within milliseconds or less (Khimich, D. *et al.*, 2005). The individual release sites appear to be controlled by few active $Ca_V1.3$ Ca^{2+} channels in nanometer proximity, which activate rapidly upon depolarization and drive vesicle fusion at near saturating speed (Ca^{2+} nanodomain control). The released glutamate rapidly opens postsynaptic alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-type glutamate receptors (Glowatzki, E. and Fuchs, P. A., 2002), which are clustered at the postsynaptic density. Excitatory postsynaptic currents (EPSCs) measured in the nerve terminals display both rapid rise (<0.50 ms) and rapid decay (<2 ms) enhancing nerve spike generation at short latency and the ability to discharge again at short intervals. Synchronous transmission of nerve impulses is optimized by their relatively uniform fiber diameter and corresponding similar conduction velocity. When the nerve impulses reach the first node of Ranvier, conduction is speeded by becoming saltatory.

Mechanisms enhancing temporal precision of auditory information coding and transmission include precise receptor potential generation, rapid Ca^{2+}-channel gating, the nanodomain control of exocytosis, parallel release of multiple vesicles at one active zone, rapid glutamate receptor signaling, and small size of postsynaptic terminal. This precise timing enables synchronization of spiking in fibers driven by one hair cell (same receptor potential). However, there are a host of opportunities for degrading neural synchrony including changes in hair cell mechanics; hair cell metabolic functions; transmitter release and reuptake; receptor sensitivity; nerve terminal nerve spike initiation; and transmission, axonal, and myelin disorders.

If there were a disorder of inner hair cells affecting transmitter release, a synaptic disorder affecting the number or sensitivity of receptor sites, or a disorder of nerve fibers affecting speed of conduction, both the synchrony of discharge and the number of fibers that were active would likely be compromised. We have modeled the general effects of such disorders in Figure 2 (gray spikes) and compared with the normal condition (black spikes). Normally the fibers all discharge at short latency with little variability. However, with a disorder of inner hair cells, the synapse, and/or the nerve fibers, the affected population's response would likely show both altered temporal patterns of discharge and overall amplitude changes. These changes are modeled in Figure 2 by reducing the number of fibers activated by 30%, and introducing in the remaining fibers a variable delay in their latency of discharge. The effects of these alterations impair both temporal synchrony and overall amplitude of response of the population of fibers and are plausible pathophysiological mechanisms accounting for the electrophysiological and psychoacoustic changes.

Figure 3 depicts how neural desynchrony could affect the appearance of the ABR (see details in Starr, A. *et al.*, 1991). The top tracing is of an ABR in which the averaging process always begins 3 ms after each click stimulus. There are five positive peaks present labeled as P1 through P5. Neural desynchrony is simulated in the lower trace by delaying the stimulus in a variable manner from between 3 and 4 ms after the start of the averaging process. Note that components P1 through P5 are markedly attenuated whereas the slow potential shift or pedestal on which the peaks arise is maintained. The attenuation of ABR peaks occurred because the neural events were made to vary in latency to cancel one another

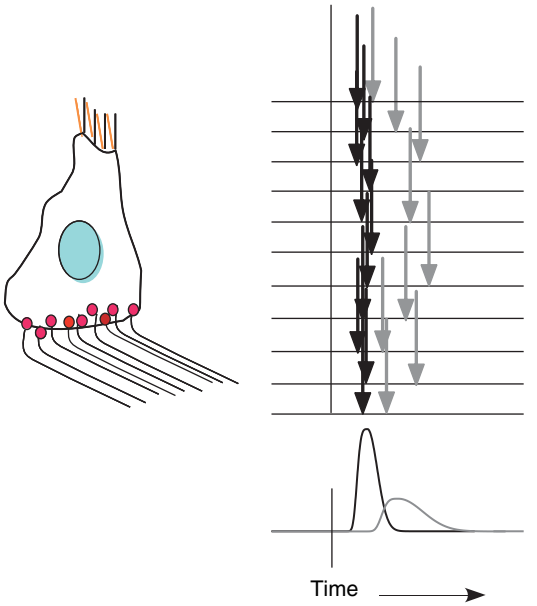

Figure 2 A representation of the patterns of activity of afferent auditory nerve fibers with synaptic connections to an inner hair cell. The onset of a transient stimulus is indicated by the vertical line below. The occurrence of fiber activity in a normally functioning system is represented by black arrows while fiber activity in an abnormal system is represented by gray arrows. The patterns of activity in the two conditions are shown below. The abnormalities of fiber activity that are represented include (a) variable delay in the latency of discharge and (b) absence of a response in 30% of the fibers. Note the short latency and synchrony of the population's response when the system is normal and the delayed latency, temporal dispersion, and reduced amplitude of the population's response when the system is abnormal. We suggest that the pattern of abnormality of activity would be similar whether the disorder were at inner hair cell, the synapse including neurotransmitter release, reuptake and binding to receptor sites, or in the nerve fibers. However, the extent of latency delay and variability as well as in the proportion of fibers that are activated would vary according to the type and extent of the pathological processes.

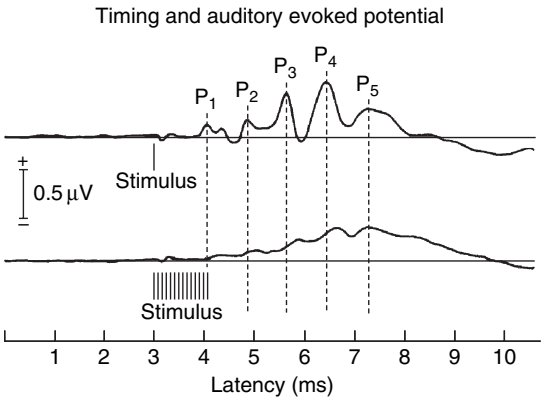

Figure 3 The effect of desynchrony on the ABR. The recordings were obtained from a cat when the stimuli were applied at precisely 3 ms after the onset of the averaging process. There are five peaks identified by the polarity (P for positive) and approximate latency in milliseconds. Another ABR was constituted when the stimulus was applied in a random manner between 3 and 4 ms after the onset of the averaging process. Note the marked attenuation of the five peaks that now appear as small variations in a sustained positive shift.

in the averaging process. The slow pedestal is not affected by the introduction of such a small variation in synchrony. We expect that such an attenuation of ABR components would accompany disorders of inner hair cells, auditory nerve fibers and/or their synapses affecting desynchrony of discharge, and/or a reduction of the number of neural elements activated making the population's response difficult to distinguish from background activity.

We suggest distinguishing the clinical disorder is known as auditory neuropathy by the presumed site of disorder. If the auditory nerve were involved with sparing of the inner hair cells and their synapses, the classification as auditory nerve disorder is appropriate. The finding of concomitant peripheral or cranial neuropathies appears to be the best evidence we have now for inferring the presence of auditory nerve disease. If the inner hair cells and/or the synapses with the auditory nerve were affected with sparing of the auditory nerve, the classification as auditory synaptic disorder is appropriate. The lack of a concomitant neuropathy of peripheral and/or cranial nerves and a positive response to electrical stimulation of the auditory nerve cell bodies is the best evidence we now have to suggest the disorder is distal in the auditory periphery in the region of the inner hair cell and its synapse with auditory nerve terminals. Synaptic disorders could involve alterations in the timing and magnitude of transmitter release and/or the availability of receptor sites on the afferent nerve terminals. There are likely many instances when both auditory nerve and inner hair cells would be affected and the classification of auditory nerve disorder, unspecified may be appropriate.

3.23.6 Psychoacoustic Deficits of Auditory Neuropathy

Auditory psychoacoustics have identified the major perceptual consequences of dysfunction of the auditory nerve (Figure 4). The mean measures of

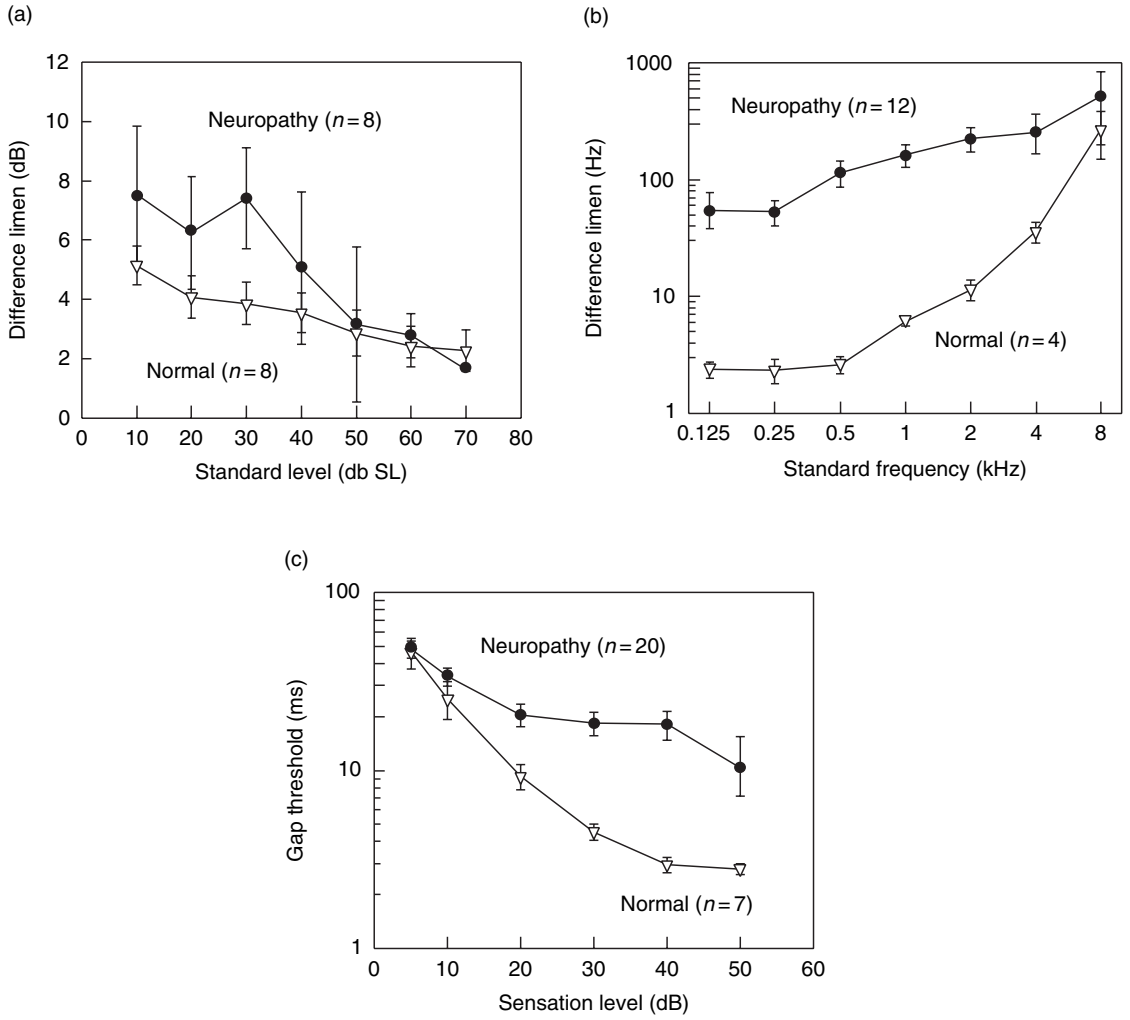

Figure 4 The means and standard errors (vertical lines) of psychoacoustic measures in patients with auditory neuropathy (filled circles) and in normal hearing subjects (unfilled, inverted triangles). The numbers of subjects tested are indicated each panel: (a) intensity discrimination; (b) frequency discrimination, and (c) gap detection. The magnitude of detection limens (DLs) for intensity discrimination was not significantly different between the two groups. In contrast, the difference limens for low frequencies up to 4 kHz were significantly higher in the auditory neuropathy group than the control group. DLs for high frequency (8 kHz) did not differ. Gap thresholds were elevated in auditory neuropathy subjects for intensities that were suprathreshold (>20 dB).

intensity discrimination (Figure 4(a)), frequency discrimination (Figure 4(b)), and temporal gap detection (Figure 4(c)) are plotted for the patients (filled circles) along with normal-hearing controls (unfilled, inverted triangles).

Although the hearing-impaired subjects tended to have greater than normal difference limen in intensity discrimination at low sensation levels, there was no overall significant difference between the affected and normal subjects. In contrast, the auditory neuropathy subjects showed significantly impaired frequency discrimination at low frequencies (125 Hz to 4 kHz) but normal difference limens at the high frequency (8 kHz). Similarly, the hearing-impaired subjects showed significantly impaired gap detection at high sensation levels (20–50 dB) but normal results at low sensation levels (5–10 dB).

Detailed description of other psychoacoustic measures has been obtained to reveal a unique pattern for persons with auditory neuropathy, in which auditory percepts dependent on temporal cues are particularly impaired whereas percepts dependent on intensity cues are preserved (Zeng, F. G. *et al.*, 2005).

Examples of impaired percepts related to temporal cues included pitch discrimination at low frequencies, temporal integration, gap detection, temporal modulation detection, backward and forward masking, signal detection in noise, binaural beats, and sound localization using interaural time differences. Examples of preserved percepts related to intensity cues included loudness discrimination, pitch discrimination at high frequencies, and sound localization using interaural level differences. These results are unique because cochlear or sensory hearing typically affects intensity related percepts (e.g., loudness recruitment) but not temporally related percepts as long as the intensity impairment is taken into account.

Objective measures of gap thresholds can also be defined using cortical potentials evoked by the interruption of a continuous noise with a silent period of different duration. (Michalewski, H. J. *et al.*, 2005). This is particularly relevant for defining temporal functions in children or adult patients who might not be able perform the normal behavioral measures of gap threshold. Figure 5 contains cortical responses to gaps from subjects with normal hearing and two individuals with auditory neuropathy and an elevated gap threshold. Note that an N100 component is clearly present in subjects with normal hearing in response to gaps as short as 5 ms whereas in the patients, N100 appears only with prolonged gap durations that approximate their psychoacoustic detection thresholds.

There were no significant differences between temporal psychoacoustic measures in subjects with a concomitant peripheral neuropathy presumed to also have a disease of the auditory nerve and those without a peripheral neuropathy presumed to have a disease affecting inner hair cells, the nerve terminals, and/or the synapse. Moreover, significant impairment in detecting tonal signals in noise has been observed in neuropathy subjects (Zeng, F. G. *et al.*, 2005). This large excess of masking, along with impaired temporal processing, contributes to the difficulty of understanding speech in noise so frequently observed in neuropathy subjects. We shall note that similar impairment in detecting tonal signals in noise has also been reported in persons who have inner hair cell loss or the so-called dead regions in cochlea (Moore, B. C., 2004). At present, we do not have a means to differentiate between the inner hair cell loss and the nerve loss.

Figure 6 presents possible mechanisms of auditory nerve responses to gaps of short duration when there are normal numbers of nerve fibers responding in a synchronous manner (Figure 6(a)) and the consequences of both impaired synchrony (Figure 6(b)) and reduced numbers of nerve fibers activated (Figure 6(c)). The normal neural response shows a clear spike pattern corresponding to the temporal gap in the stimuli. However, both the reduced neural synchrony and input will diminish this temporal

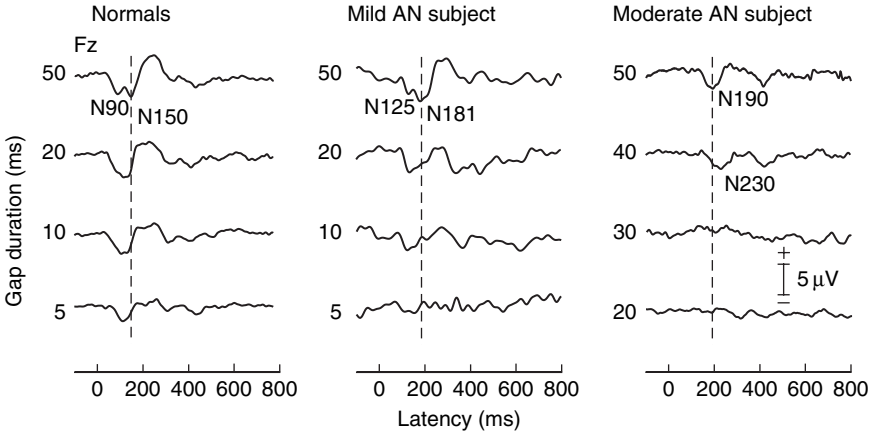

Figure 5 Cortical potentials as objective measure of gap threshold. Scalp-recorded brain potentials to gaps at 50 ms (top traces) and decreasing in duration in subsequent traces indicated on the left of each panel. In normal subjects (psychoacoustic gap threshold was 3 ms) clear N100 components indicated by dashed vertical line can be identified down to 5-ms gaps. In a subject with mild auditory neuropathy (psychoacoustic gap threshold was 8 ms), N100 can be identified at 50, 20, and 10 ms but not at 5 ms. In a subject with a moderate auditory neuropathy (AN; psychoacoustic gap threshold was 30 ms), N100 was delayed and identified at 50 and 40 ms, but not at 30 or 20 ms.

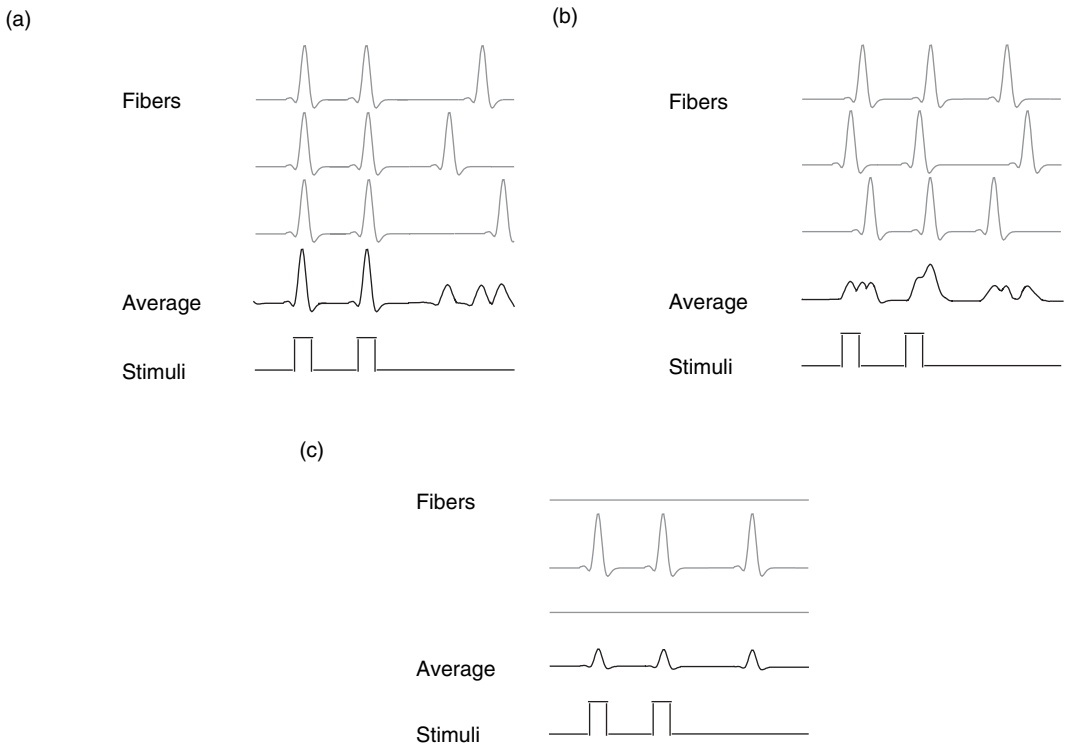

Figure 6 Population of auditory nerve fiber responses of to transient signals separated by a brief temporal gap when there is (a) normal synchrony; (b) desynchronized; and (c) deafferentation but preserved synchrony. Note that the neural representation of the two stimuli and their intervening gap are degraded when there is desynchrony or deafferentation. The condition when both desynchrony and deafferentation coexist would result in further loss of correlation with the acoustic stimuli.

gap at the neural level, making it difficult to discriminate from spontaneous background activity.

At present, we are lacking effective means to differentiate between these two models, as they all tend to show similar audiological, electrophysiological, and behavioral symptoms. Future studies using electric stimulation of the auditory nerve via a cochlear implant (CI) might be able to differentiate these two models, as selective loss of inner hair cells or dysfunctional synapses should not present a significant problem in electric stimulation, which bypasses these structures and activates the neuron's cell body or axon directly.

Clinical management of auditory neuropathy is difficult and not yet standardized. Because of the lack of success with conventional hearing aids, CIs have become the choice of treatment for many clinicians (Shallop, J. K. *et al.*, 2001). The psychoacoustic results suggest that novel features may need to be introduced in hearing aids in order for them to have any chance to help persons with neural hearing loss. One new feature would be to perform modulation expansion as opposed to compression in a typical hearing aid to compensate for the impaired temporal processing abilities. Another feature would be to perform upward frequency shift as opposed to downward frequency shift to take advantage of relatively normal pitch processing at high frequencies in persons with auditory neuropathy.

Individuals with disorders of the inner hair cells or their synapses appear especially likely to benefit from CIs. For instance, auditory neuropathy accompanying mutations of the otoferlin gene (*OTOF*; Rodriquez-Ballesteros, M. *et al.*, 2003; Varga, R. *et al.*, 2003) respond well to cochlear implantation. It is likely that in this disorder there are sufficient numbers of auditory nerve fibers and ganglion cells present capable of responding to electrical stimulation.

Cochlear implantation has also benefited subjects with a dominantly inherited deafness without peripheral nerve involvement (Starr, A. *et al.*, 2004). These subjects initially have absent ABRs and preserved OAEs and CMs. The latter two measures become lost within a few years of onset reflecting an

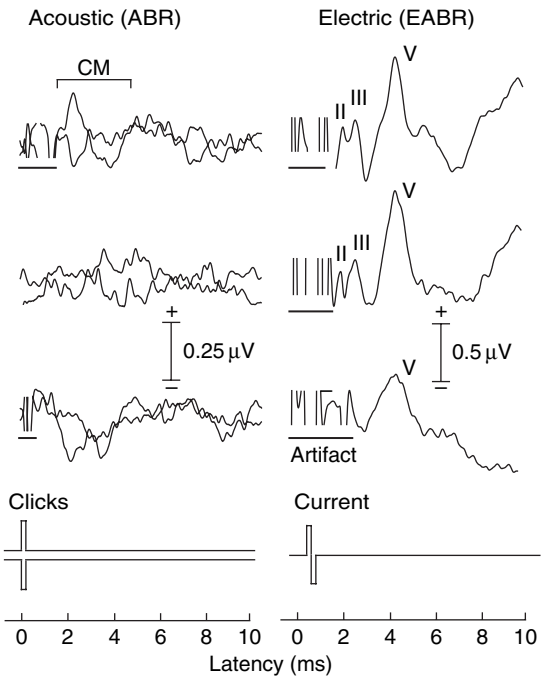

Figure 7 ABRs in three family members with a dominantly inherited disorder producing auditory nerve dysfunction (Starr, A. *et al.*, 2004). Prior to cochlear implantation, ABRs in response to acoustic stimulation do not show neural responses but cochlear microphonics (CM) were identified in one. After implantation electrical stimulation applied through the implant evoked large-amplitude neural components in all three. The artifacts of stimulation are indicated by the horizontal line for both the acoustic and electrical stimulation. Gap detection and speech comprehension improved remarkably following implantation.

involvement of OHCs only later in the course of the disorder. It is likely that the disorder affects inner hair cells/nerve terminals allowing the CI to provide striking benefits. Figure 7 contains ABRs and electrically evoked ABRs (EABRs) from three affected family members before and after implantation. The absence of acoustic ABRs prior to implantation contrasts with the well-developed EABRs after implantation. The subjects' abnormalities of gap thresholds and speech comprehension were also benefited after implantation.

3.23.7 Molecular Mechanisms of Auditory Neuropathy

We will present examples of mice (see Table 1) with genetically engineered defects affecting inner hair cells, synapses, or auditory nerve functions that provide an opportunity to define how specific genes alter auditory functions. Audiological tests of these mutants can identify similarities and differences to auditory neuropathies in humans. There is a particular need to develop both behavioral and objective measures of specific features of the accompanying auditory deficits such as cortical potential measures in response to gaps (Michalewski, H. J. *et al.*, 2005). We expect that characterizing the disorder at the cellular and molecular levels in these mutants may facilitate the development of tests and therapies in human disorders of hearing. The auditory findings on selective examples of gene mutants with various forms of auditory nerve dysfunction are presented below.

3.23.7.1 Inner Hair Cell Channelopathy-Knockout of the Inner Hair Cell $Ca_V1.3$

The molecular identity of the mammalian hair cell Ca^{2+} channel was proven to be $Ca_V1.3$ by a knockout experiment by Platzer J. *et al.* (2000) and Dou H. *et al.* (2004). The Ca^{2+} current of $Ca_V1.3^{-/-}$ inner hair cells is reduced by ~90% in inner hair cells causing a major defect of inner hair cell exocytosis (Figure 8(b); Brandt, A. *et al.*, 2003). $Ca_V1.3^{-/-}$ mice have absent ABRs (Figure 8(c)). Inner hair cells maintain their morphology for at least 2 months after birth but progressively loose their afferent synapses (Nemzou *et al.*, 2006). OHCs at the basilar turn of the cochlear are morphologically preserved for several weeks and produce high-frequency distortion product OAEs. In contrast, OHCs at the apical coil lose their stereovilli and tend to degenerate. There also appears to be an associated reduction of the numbers of surviving spiral ganglion neurons (Glueckert, R. *et al.*, 2003; Dou, H. *et al.*, 2004). A massive exocytosis of transmitter can still be elicited in inner hair cells by artificially increasing the cytosolic Ca^{2+} concentration (Brandt, A. *et al.*, 2003). Together, the results indicate that the lack of inner hair cell $Ca_V1.3$ channels disrupts the coupling of receptor potential and transmitter release. Thus a profound dysfunction of auditory nerve occurs in animals in the neonatal period with a gene defect disabling Ca^{2+} influx into inner hair cell with consequences of disrupting synaptic transmitter release. The disorder is progressive and can also affect the survival of both OHCs and auditory nerve.

Table 1 Animal examples of the variety of auditory nerve dysfunctions

	Primary mechanism	*Animal model (examples)*	*Human disease*	*OAE/CM*	*ABR*	*Morphology*	*Cellular phenotype/ molecular defect*
Disorders of inner hair cells and their synapses	IHC channelopathy	$Ca_V1.3$ KO [a,b,c]		+	Absent	Stereociliar defect of apical OHCs, age-dependent loss of apical OHCs, reduction of SGN	~90% reduction of Ca^{2+} current. Near complete block of IHC transmitter release
Auditory synaptopathy	Defect of presynaptic active zone	Bassoon KO [d]		+	Abnormal	No obvious morphological changes	Defect of synaptic ribbon anchorage at the active zone. Selective defect of synchronous transmitter release
	Inner hair cell vesicle fusion IHC transmitter release	To be generated Otoferlin KO (Roux *et al.*, Cell 2006)	Otoferlin inner hair cell disorders	+	Absent	Normal synaptogenesis, rapid loss of synapses	Major reduction of IHC transmitter release, defect of late step of exocytosis
	Defect of postsynaptic zone	Tubby mouse[e]	Profound prelingual deafness DFNB9				
Disorders of auditory nerve	Mislocalization of ion channels at axon initial segments and nodes of Ranvier	β-4-Spectrin-mutants[f,g]		+	Abnormal	Ultrastructural changes of nerve fibers	Impaired scaffolding of channels and cytoskeletal anchorage
Auditory neuropathy							Impaired nerve conduction
	Demyelination	PMP22-mutants MPZ-mutants[h,i]	Hereditary neuropathies		Abnormal	Demyelination, loss of dendrites, SGN reduction	Impaired nerve conduction due to short internodes, demyelinated axon segments, loss of SGN
	Axon/SGN loss	Dominant-negative erbB4-mutant[j]		+	Abnormal	SGN loss	Loss of axons and SGN

+, present; ABR, auditory brainstem response; CMs, cochlear microphonics; IHC, inner hair cell; KO, knockout; OAEs, otoacoustic emissions; OHC, outer hair cell; SGN, spiral ganglion neurons;
[a]Platzer J. *et al*. (2000).
[b]Brandt A. *et al*. (2003).
[c]Dou H. *et al*. (2004).
[d]Khimich D. *et al*. (2005).
[e]Noben-Trauth K. *et al*. (1996).
[f]Parkinson N. J. *et al*. (2001).
[g]Lacas-Gervais S. *et al*. (2004).
[h]Zhou R. *et al*. (1995).
[i]Zhou *et al*. (1995).
[j]Stankovic K. *et al*. (2004).

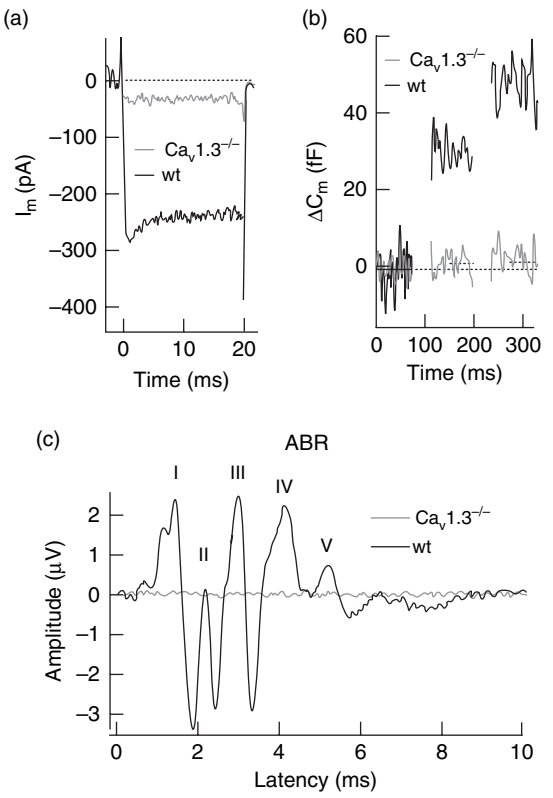

Figure 8 Auditory synaptic nerve dysfunction in a mutant mouse ($Ca_V1.3$-deficient) accompanying profound impairment of hair cell transmitter release due to loss of Ca^{2+} influx. (a) Voltage-gated Ca^{2+}currents in normal (Im: membrane current) (black) and a $Ca_V1.3$-deficient (gray) inner hair cells. There is a major reduction of Ca^{2+} influx in the mutant (~90%). (b) The absence of exocytic capacitance changes (ΔC_m) to paired depolarizations in a $Ca_V1.3$-deficient inner hair cell compared to the normal response. c, ABRs from a 3-week-old wild-type (WT) mouse (black trace) showing normal neural components and the absence neural components in a $Ca_V1.3$-deficient mouse (gray trace).

3.23.7.2 Impaired Inner Hair Cell Transmitter Release

Bassoon is a large matrix protein, which helps to anchor ribbons to the hair cell active synaptic zones. Quantitative assessment of the number of synapse-anchored ribbons of mature mutant mice (stained as green in Figures 9(a) and 9(b)) showed that inner hair cells on average contained one anchored ribbon compared to 10 ribbons in wild-type (WT) animals (Khimich, D. *et al.*, 2005). This reduction in synaptic function is accompanied by abnormal ABRs (Figure 9(c)) showing a marked attenuation and delay of wave I whereas subsequent components were affected only slightly. The thresholds for evoking the ABR were elevated up to 30 dB (Figure 9(d)). OHC activity reflected by CMs and distortion product OAEs were normal. Patch-clamp analysis of inner hair cell presynaptic function revealed a reduced readily releasable pool of synaptic vesicles and a slight reduction of the Ca^{2+} current in ribbon-deficient inner hair cells (Figures 9(e) and 9(f)). Thus, a reduction of ribbon-anchored synapses results in auditory nerve dysfunction reflected by impaired spiral ganglion activation (wave I) without changes in OAEs. The relative preservation of activity arising in brainstem portions of the auditory pathway may indicate that the change of synchrony in the auditory periphery is mild and can be compensated by central auditory mechanisms.

3.23.7.3 Auditory Nerve Ion Channel Displacement

The location of voltage-gated sodium channels in clusters at the nodes of Ranvier in auditory nerves is essential for normal saltatory propagation of action potentials along axons. Beta-4 spectrins are cytoskeletal proteins, which are involved in the positioning and linkage of voltage-gated sodium and potassium channels at the nodes of Ranvier (Bennett, V. and Baines, A. J., 2001). Beta-4 spectrin mutants are also known as Quivering mice because of their abnormal motor behaviors. The alterations in the locations of the voltage-gated channels are shown in Figures 10(d)–10(f). These animals can also have hearing impairments that vary with the mutation. Spontaneous mouse mutants with truncated beta-4 spectrin showed an intriguing correlation of the length of the remaining spectrin protein with the transmission along the auditory pathway (Parkinson, N. J. *et al.*, 2001). In the animals most severely affected only a wave I was present. Auditory studies in less affected mutant animals (Lacas-Gervais, S. *et al.*, 2004) showed auditory thresholds were unaffected (Figure 10(c)) whereas there was progressive delay of ABR peaks consistent with involvement of conduction along the brainstem auditory pathway (Figures 10(a) and 10(b)).

The delay in latency increased at higher stimulation rates and could be consistent with conduction deficits and/or conduction block in the affected fibers.

3.23.7.4 Auditory Nerve Fiber Myelin Disorder

Defects of genes coding for myelin proteins result in hereditary neuropathy (review in Suter, U. and

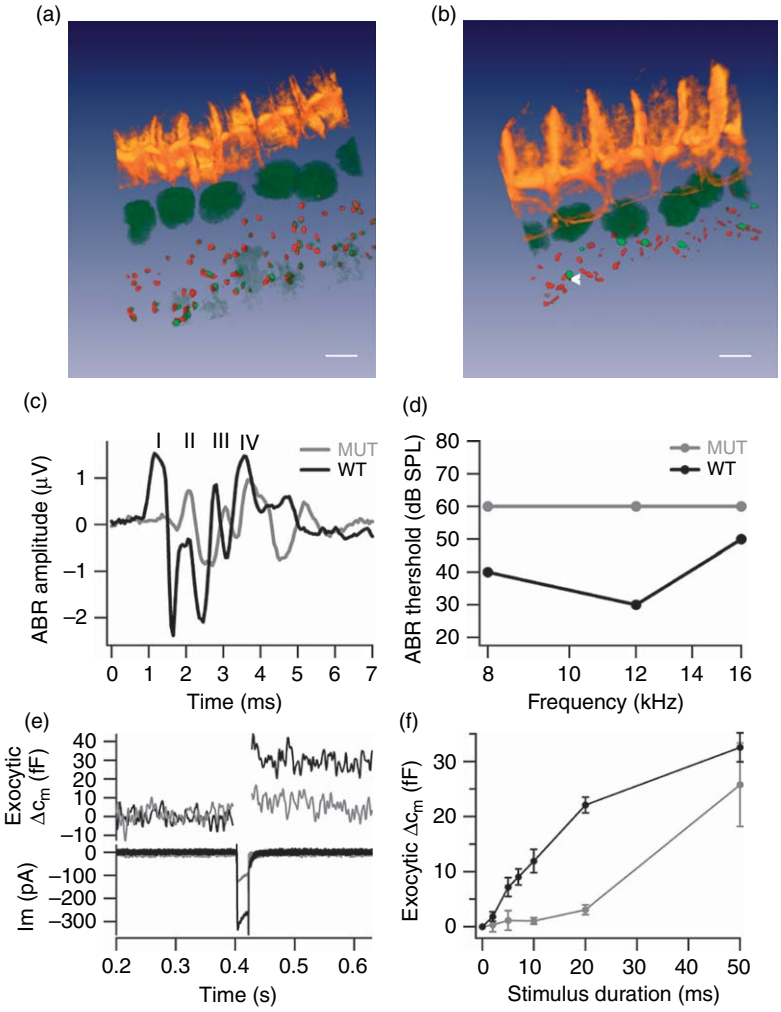

Figure 9 Auditory nerve dysfunction accompanying reduction in the numbers of synaptic ribbons in inner hair cells, the Bassoon mutant. a and b, immunostaining for RIBEYE/CtBP-2 (green): labeling ribbons and nuclei, postsynaptic glutamate receptors (red) adjacent to inner hair cell ribbons. Inner hair cells in mutants (MUT) (a) show fewer ribbon-postsynapstic pairs (arrow) than in wild-type (WT) animals (b). Actin filaments in. . . were labeled with Phalloidin and rendered gold. The apical part of inner hair cell and the adjacent pillar cells are labeled gold. Scale bar: 5 μm. (c) ABR of a representative pair of MUT (gray) and WT (black) mice in response to suprathreshold clicks (80 dB peSPL). Note that wave I was delayed and profoundly attenuated in the MUTs whereas the subsequent waves were only slightly attenuated but delayed in latency. (d) ABR threshold as function of frequency. The MUTs have normal otoacoustic emissions (not shown). (e) Representative Ca^{2+} currents and C_m changes recorded from WT and MUT inner hair cells (20 ms step depolarization). (f) Kinetics of exocytosis constructed from ΔC_m of the same inner hair cells in response to depolarization of varying durations showing depressed response in the MUT. SPL, sound pressure level; Im, membrane current; ΔC_m, exocytic membrane capacitance change.

Scherer, 2003). For example, mutations of the PMP22 gene cause hypomyelination, impaired nerve conduction and consequently neural hearing loss (Verhagen, W. I. *et al.*, 2005) in human Charcot–Marie–Tooth disease (Suter, U. and Scherer, S. S., 2003). Animal models with *PMP22* gene mutations have been described with altered auditory functions. The mutant known as Trembler because of their motor abnormalities shows reduced amplitudes and latency delay of ABR components. There are alterations of myelination of auditory nerve accompanied by a delayed spiral ganglion loss (Zhou, R. *et al.*, 1995a; 1995b). OHC functions have not been defined. These mutant animals have auditory nerve dysfunction due to a nerve disorder affecting myelin.

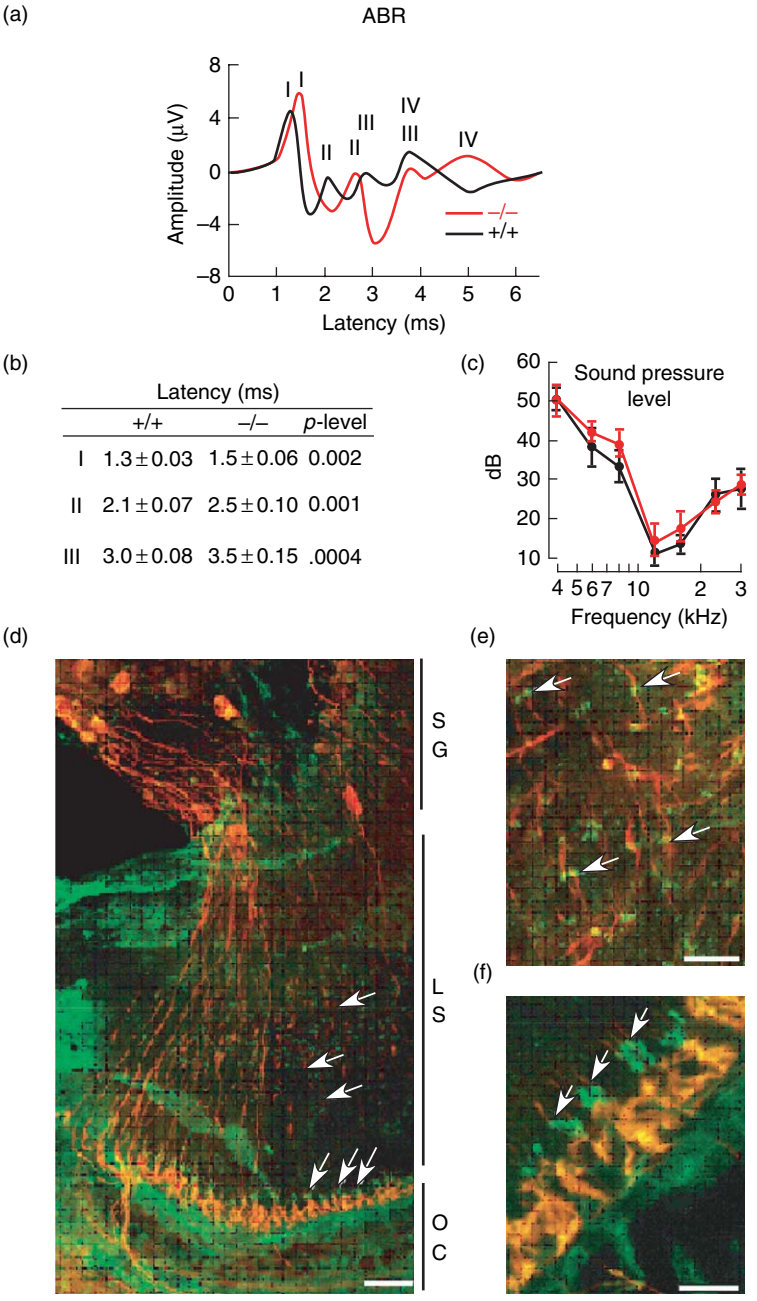

Figure 10 Auditory nerve dysfunction accompanying reduction in the numbers of synaptic ribbons in inner hair cells, the Bassoon mutant. (a) and (b) immunostaining for RIBEYE/CtBP-2 (green): labeling ribbons and nuclei, glutamate receptors (red) adjacent to IHC ribbons. Inner hair cells in mutants (a) show fewer ribbon-postsynapstic pairs (arrow) than in wild type animals (b). The apical part of inner hair cell and the adjacent pillar cells are labeled gold. Scale bar: 5 μm. (c) ABR of a representative pair of mutant (grey) and wild type (WT) (black) mice in response to suprathreshold clicks (80 dB peSPL). Note that Wave I was delayed and profoundly attenuated in the mutant whereas the subsequent waves were only slightly attenuated but delayed in latency. (d) ABR threshold as function of frequency. The mutants have normal otoacoustic emissions. (e) Representative Ca^{2+} currents and C_m changes recorded from WT and mutant IHCs (20 ms step depolarization). (f) Kinetics of exocytosis constructed from ΔC_m of the same IHCs in response to depolarization of varying durations showing depressed response in the wild type.

3.23.7.5 Loss of Spiral Ganglion Neurons

Spiral ganglion neurons may be affected as both a primary and a secondary effect of gene mutations. Recent data demonstrated that the survival of spiral ganglion neurons depends on a complex regulation involving the neuregulin-erbB system and neurotrophin signaling (Stankovic, K. *et al.*, 2004). Their study showed a primary expression of erbB in the supporting cells of the organ of Corti. Disabling the erbB receptor function results in a rapid and ~80% loss of spiral ganglion neurons. Immediately prior to the neuronal loss, downregulation of cochlear neurotrophin-3 expression occurred, which appears to be important for ganglion cell maintenance. The audiological findings are consistent with auditory neuropathy showing absent or profoundly abnormal ABRs and preserved OAEs. Both IHCs and OHCs appear to be little affected. This gene mutation results in auditory nerve dysfunction consistent with loss of spiral ganglion cells without other peripheral or cranial neuropathies.

3.23.8 Conclusions

There has been considerable advance in identifying and characterizing auditory nerve dysfunction in humans. We have highlighted physiological criteria for defining the disorder and identified the diversity of affected structures in the auditory periphery that, when affected, can be accompanied by auditory neuropathy. Psychoacoustic results show that the deficits of auditory nerve dysfunctions primarily affect those percepts dependent on temporal cues. The development of experimental animal models with auditory nerve dysfunction has begun to provide insights into basic molecular mechanisms of the disorders and will hopefully lead to the development of treatment therapies.

Acknowledgments

This research was supported in part by grants DC-02618 (Starr) and DC-02267 (Zeng) from the National Institutes of Health, and the MPG (Tandemproject) and DFG (CMPB) to T Moser.

References

Amatuzzi, M. G., Northrop, C., Liberman, M. C., Thornton, A., Halpin, C., Herrmann, B., Pinto, L. E., Saenz, A., Carranza, A., and Eavey, R. D. 2001. Selective inner hair cell loss in premature infants and cochlear pathological patterns from neonatal intensive care unit autopsies. Arch. Otolaryngol. Head Neck Surg. 127, 629–636.

Bennett, V. and Baines, A. J. 2001. Spectrin and ankyrin-based pathways: metazoan inventions for integrating cells into tissues. Physiol. Rev. 81, 1353–1392.

Berlin, C. I., Bordelon, J., St John, P., Wilensky, D., Hurley, A., Kluka, E., and Hood, L. J. 1998. Reversing click polarity may uncover auditory neuropathy in infants. Ear Hear. 19, 37–47.

Berlin, C. I., Hood, L. J., Cecola, R. P., Jackson, D. F., and Szabo, P. 1993. Does type I afferent neuron dysfunction reveal itself through lack of efferent suppression? Hear. Res. 65, 40–50.

Berlin, C. I., Hood, L. J., Morlet, T., Rose, K., and Brashears, S. 2003. Auditory neuropathy/dys-synchrony: diagnosis and management. Ment. Retard. Dev. Disabil. Res. Rev. 9, 225–231.

Brandt, A., Striessnig, J., and Moser, T. 2003. $Ca_V1.3$ channels are essential for development and presynaptic activity of cochlear inner hair cells. J. Neurosci. 23, 10832–10840.

Brownell, W. E. 1984. Microscopic observation of cochlear hair cell motility. Scan. Electron Microsc. Pt 3, 1401–1406.

Davis, H. and Hirsh, S. K. 1979. A slow brain stem response for low-frequency audiometry. Audiology 18, 445–461.

Dou, H., Vazquez, A. E., Namkung, Y., Chu, H., Cardell, E. L., Nie, L., Parson, S., Shin, H. S., and Yamoah, E. N. 2004. Null mutation of alpha1D Ca^{2+} channel gene results in deafness but no vestibular defect in mice. J. Assoc. Res. Otolaryngol. 5, 215–226.

Doyle, K. J., Sininger, Y., and Starr, A. 1998. Auditory neuropathy in childhood. Laryngoscope 108, 1374–1377.

Glowatzki, E. and Fuchs, P. A. 2002. Transmitter release at the hair cell ribbon synapse. Nat. Neurosci. 5, 147–154.

Glueckert, R., Wietzorrek, G., Kammen-Jolly, K., Scholtz, A., Stephan, K., Striessnig, J., and Schrott-Fischer, A. 2003. Role of class D L-type Ca^{2+} channels for cochlear morphology. Hear. Res. 178, 95–105.

Hallpike, C. S., Harriman, D. G., and Wells, C. E. 1980. A case of afferent neuropathy and deafness. J. Laryngol. Otol. 94, 945–964.

Hecox, K. and Galambos, R. 1974. Brain stem auditory evoked responses in human infants and adults. Arch. Otolaryngol. 99, 30–33.

Hood, L. J. and Berlin, C. I. 2001. Auditory Neuropathy (Auditory Dys-synchrony) Disables Efferent Suppression of Otoacoustic Emissions. In: Auditory Neuropathy: A New Perspective on Hearing Disorders (*eds*. Y. Sininger and A. Starr), pp. 183–202. Singular.

Kaga, K., Kitazumi, E., and Kodama, K. 1979. Auditory brain stem responses of kernicterus infants. Int. J. Pediatr. Otorhinolaryngol. 1, 255–264.

Kemp, D. T. 1978. Stimulated acoustic emissions from within the human auditory system. J. Acoust. Soc. Am. 64, 1386–1391.

Khimich, D., Nouvian, R., Pujol, R., Tom Dieck, S., Egner, A., Gundelfinger, E. D., and Moser, T. 2005. Hair cell synaptic ribbons are essential for synchronous auditory signaling. Nature 434, 889–894.

Kraus, N., Ozdamar, O., Stein, L., and Reed, N. 1984. Absent auditory brain stem response: peripheral hearing loss or brain stem dysfunction? Laryngoscope 94, 400–406.

Lacas-Gervais, S., Guo, J., Strenzke, N., Scarfone, E., Kolpe, M., Jahkel, M., De Camilli, P., Moser, T.,

Rasband, M. N., and Solimena, M. 2004. BetaIVSigma1 spectrin stabilizes the nodes of Ranvier and axon initial segments. J. Cell Biol. 166, 983–990.

Lenhardt, M. L. 1981. Childhood central auditory processing disorder with brainstem evoked response verification. Arch. Otolaryngol. 107, 623–625.

Martin, W. H., Pratt, H., and Schwegler, J. W. 1995. The origin of the human auditory brain-stem response wave II. Electroencephalogr. Clin. Neurophysiol. 96, 357–370.

Melcher, J. R., Knudson, I. M., Fullerton, B. C., Guinan, J. J., Jr., Norris, B. E., and Kiang, N. Y. 1996. Generators of the brainstem auditory evoked potential in cat. I. An experimental approach to their identification. Hear. Res. 93, 1–27.

Michalewski, H. J., Starr, A., Nguyen, T. T., Kong, Y. Y., and Zeng, F. G. 2005. Auditory temporal processes in normal-hearing individuals and in patients with auditory neuropathy. Clin. Neurophysiol. 116, 669–680.

Moore, B. C. 2004. Dead regions in the cochlea: conceptual foundations, diagnosis, and clinical applications. Ear Hear. 25, 98–116.

Noben-Trauth, K., Naggert, J. K., North, M. A., and Nishina, P. M. 1996. A candidate gene for the mouse mutation tubby. Nature 380, 534–538.

Parkinson, N. J., Olsson, C. L., Hallows, J. L., McKee-Johnson, J., Keogh, B. P., Noben-Trauth, K., Kujawa, S. G., and Tempel, B. L. 2001. Mutant beta-spectrin 4 causes auditory and motor neuropathies in quivering mice. Nat. Genet. 29, 61–65.

Platzer, J., Engel, J., Schrott-Fischer, A., Stephan, K., Bova, S., Chen, H., Zheng, H., and Striessnig, J. 2000. Congenital deafness and sinoatrial node dysfunction in mice lacking class D L-type Ca^{2+} channels. Cell 102, 89–97.

Rapin, I. and Gravel, J. 2003. ''Auditory neuropathy'': physiologic and pathologic evidence calls for more diagnostic specificity. Int. J. Pediatr. Otorhinolaryngol. 67, 707–728.

Rodriguez-Ballesteros, M., del Castillo, F. J., Martin, Y., Moreno-Pelayo, M. A., Morera, C., Prieto, F., Marco, J., Morant, A., Gallo-Teran, J., Morales-Angulo, C., Navas, C., Trinidad, G., Tapia, M. C., Moreno, F., and del Castillo, I. 2003. Auditory neuropathy in patients carrying mutations in the otoferlin gene (OTOF). Hum. Mutat. 22, 451–456.

Ropper, A. H. and Chiappa, K. H. 1986. Evoked potentials in Guillain-Barré syndrome. Neurology 36, 587–590.

Satya-Murti, S., Cacace, A., and Hanson, P. 1980. Auditory dysfunction in Friedreich ataxia: result of spiral ganglion degeneration. Neurology 30, 1047–1053.

Shallop, J. K., Peterson, A., Facer, G. W., Fabry, L. B., and Driscoll, C. L. 2001. Cochlear implants in five cases of auditory neuropathy: postoperative findings and progress. Laryngoscope 111, 555–562.

Sininger, Y. and Oba, S. 2001. Patients With Auditory Neuropathy: Who Are They and What Can They Hear? In: Auditory Neuropathy: A New Perspective on Hearing Disorders (*eds*. Y. Sininger and A. Starr), pp. 15–35. Singular.

Spoendlin, H. 1974. Optic cochleovestibular degenerations in hereditary ataxias. II. Temporal bone pathology in two cases of Friedreich's ataxia with vestibule-cochlear disorders. Brain 97, 41–48.

Stankovic, K., Rio, C., Xia, A., Sugawara, M., Adams, J. C., Liberman, M. C., and Corfas, G. 2004. Survival of adult spiral ganglion neurons requires erbB receptor signaling in the inner ear. J. Neurosci. 24, 8651–8661.

Starr, A. 2001. The Neurology of Auditory Neuropathy. In: Auditory Neuropathy: A New Perspective on Hearing Disorders (*eds*. Y. Sininger and A. Starr), pp. 37–49. Singular.

Starr, A. and Achor, J. 1975. Auditory brain stem responses in neurological disease. Arch. Neurol. 32, 761–768.

Starr, A. and Hamilton, A. E. 1976. Correlation between confirmed sites of neurological lesions and abnormalities of far-field auditory brainstem responses. Electroencephalogr. Clin. Neurophysiol. 41, 595–608.

Starr, A., Isaacson, B., Michalewski, H. J., Zeng, F. G., Kong, Y. Y., Beale, P., Paulson, G. W., Keats, B. J., and Lesperance, M. M. 2004. A dominantly inherited progressive deafness affecting distal auditory nerve and hair cells. J. Assoc. Res. Otolaryngol. 5, 411–426.

Starr, A., McPherson, D., Patterson, J., Don, M., Luxford, W., Shannon, R., Sininger, Y., Tonakawa, L., and Waring, M. 1991. Absence of both auditory evoked potentials and auditory percepts dependent on timing cues. Brain 114, 1157–1180.

Starr, A., Michalewski, H. J., Zeng, F. G., Fujikawa-Brooks, S., Linthicum, F., Kim, C. S., Winnier, D., and Keats, B. 2003. Pathology and physiology of auditory neuropathy with a novel mutation in the MPZ gene (Tyr145->Ser). Brain 126, 1604–1619.

Starr, A., Picton, T. W., and Kim, R. 2001a. Pathophysiology of Auditory Neuropathy. In: Auditory Neuropathy: A New Perspective on Hearing Disorders (*eds*. Y. Sininger and A. Starr), pp. 67–82. Singular.

Starr, A., Picton, T. W., Sininger, Y., Hood, L. J., and Berlin, C. I. 1996. Auditory neuropathy. Brain 119, 741–753.

Starr, A., Sininger, Y., Nguyen, T., Michalewski, H. J., Oba, S., and Abdala, C. 2001b. Cochlear receptor (microphonic and summating potentials, otoacoustic emissions) and auditory pathway (auditory brain stem potentials) activity in auditory neuropathy. Ear Hear. 22, 91–99.

Suter, U. and Scherer, S. S. 2003. Disease mechanisms in inherited neuropathies. Nat. Rev. Neurosci. 4, 714–726.

Varga, R., Kelley, P. M., Keats, B. J., Starr, A., Leal, S. M., Cohn, E., and Kimberling, W. J. 2003. Non-syndromic recessive auditory neuropathy is the result of mutations in the otoferlin (OTOF) gene. J. Med. Genet. 40, 45–50.

Verhagen, W. I., Huygen, P. L., Gabreels-Festen, A. A., Engelhart, M., van Mierlo, P. J., and van Engelen, B. G. 2005. Sensorineural hearing impairments in pateints with Pmp22 duplication, deletion, and frame shift mutations. Otol. Neurotol. 26, 405–414.

Worthington, D. W. and Peters, J. F. 1980. Quantifiable hearing and no ABR: paradox or error? Ear Hear. 1, 281–285.

Yasunaga, S., Grati, M., Cohen-Salmon, M., El-Amraoui, A., Mustapha, M., Salem, N., El-Zir, E., Loiselet, J., and Petit, C. 1999. A mutation in OTOF, encoding otoferlin, a FER-1-like protein, causes DFNB9, a nonsyndromic form of deafness. Nat. Genet. 21, 363–369.

Zeng, F. G., Kong, Y. Y., Michalewski, H. J., and Starr, A. 2005. Perceptual consequences of disrupted auditory nerve activity. J. Neurophysiol. 93, 3050–3063.

Zeng, F. G., Oba, S., Garde, S., Sininger, Y., and Starr, A. 1999. Temporal and speech processing deficits in auditory neuropathy. Neuroreport 10, 3429–3435.

Zhou, R., Abbas, P. J., and Assouline, J. G. 1995a. Electrically evoked auditory brainstem response in peripherally myelin-deficient mice. Hear. Res. 88, 98–106.

Zhou, R., Assouline, J. G., Abbas, P. J., Messing, A., and Gantz, B. J. 1995b. Anatomical and physiological measures of auditory system in mice with peripheral myelin deficiency. Hear. Res. 88, 87–97.